THE MÜTTER LECTURES ON SELECTED TOPICS IN SURGICAL PATHOLOGY.

SERIES OF 1890-1.[1]

By ROSWELL PARK, A.M., M.D.,

OF BUFFALO,

PROFESSOR OF SURGERY, MEDICAL DEPARTMENT, UNIVERSITY OF BUFFALO; SURGEON TO THE BUFFALO GENERAL HOSPITAL, ETC.

LECTURE I.

INTRODUCTION.—*Ever-growing importance of the study of Surgical Pathology. Lessons to be learned from the life-work of eminent observers.*

The inflammatory process: its varieties. Granulomatous inflammation. Thrombi; varieties and how formed. Traumatic anæmia. Hæmoglobin and oligochromæmia. Aerobic and anaerobic life of the organism, and chemical products of the same. Ptomaines and leucomaines; classification and definition of same. Toxines. Proof of formation of ptomaines by bacterial action.

Classification of infectious diseases. Surgical infections and discussion of conditions predisposing to them. Embolism as one of these conditions. General depression of vitality. Local depression. Influence of inflammation; of cold; of injury.

IT WILL not be amiss if at the opening of the present course, the lecturer prefaces its more technical portion with a few words concerning the present advanced stage of surgical progress, and the causes which have contributed thereto. If we call before our minds the really great surgeons of to-day, or of the present generation, and ask ourselves by virtue of what particular attributes they have become great, we shall satisfy ourselves that they are not only good anatomists, and men of

[1]Delivered before the College of Physicians, Philadelphia, December, 1890.

broad general attainments, not only are they all—or nearly all—brilliant operators; but more, much more than this, they are all good physiologists, and especially, good *pathologists*.

Sound and tenable pathology is to-day as essential for the surgeon as for the physician; one needs it as much as the other. If at this time there is any one respect in which the continental surgeons eclipse those of our country, it is in this. Better anatomists they are not—certainly not better operators—for the most part not as good. But by virtue of their early training, and by the influence of tradition and surrounding, they are reared in an atmosphere—so to speak—of pathological interest and lore; they imbibe it as part of their daily increment of knowledge, and hence they acquire whatever element of superiority they may enjoy over their American *confreres*. It is hardly my business, nor is it my purpose here to try to point out the reasons for this state of affairs, nor to suggest remedies.

But I can do no greater service to the younger men to whose notice these words may come than by every means, and by every argument in my power, impressing and insisting upon their conviction that the early years of their medical studies constitute the golden opportunity for laying in that store of elementary knowledge of normal and morbid physiology, *i. e.*, pathology, and of that familiarity with instruments of research and of technical methods, which shall prove of inestimable advantage to them a little later. How many men whom we could name at once have fallen just short of greatness because of deficiency in this respect! And what a magnificent future lies before succeeding generations of surgeons, if they will but properly prepare themselves for it!

Langenbeck, who well deserved the proud title of Nestor of recent German surgeons, did no greater service for surgery than when he brought to his professional surgical chair the practical knowledge of physiology which he had acquired by teaching it, and introduced into his akiurgical instruction the experimental method as the two never had been combined before. By this method, as it was practiced by him and his pupils, there was brought about almost a second *renaissance* of surgery; while its conspicuous advantages turned the tide of

surgical travelers from London and Paris toward Germany, and put German teaching—of this branch of the healing art—so far ahead that even to-day those who would not go to Germany have no need to leave this country for the acquisition of such knowledge. Outside of Germany the same is true in little less noticeable degree. The two London surgeons, most honored of all, at home and abroad, are Sir James Paget and Mr. Jonathan Hutchinson; and of the French no man's opinion carries more weight than does that of Verneuil or of Ollier. Yet if I were asked whether these men rank higher as surgeons or as pathologists, I should unhesitatingly say as the latter. And no better illustration of the soundness of my position did America ever afford than was furnished here in your own city by the distinguished Gross. No one at all familiar with his life and work can deny that his greatness and his accuracy as a surgeon were in very large measure due to the attention he paid to pathology during his early years, or indeed all his life. A cursory examination of his early textbook on this subject will be convincing in this respect.

Aside from the ordinary knowledge and ability, which, by common consent, every surgeon deserving the name should possess, it seems to me that the cultus of the day demands that hereafter none should be deemed competent to practice surgery who have not had competent and abundant training along the lines of

1. Experimental physiology and pathology.
2. Pathological histology and general pathology, including
3. Bacteriology.

It cannot be considered as improper or too personal if I mention a few individuals among living surgeons, whose work illustrates forcibly the advantage of such training. I know of no one who has more happily combined the dexterity of the accomplished surgeon with the training and education of the expert physiologist than Mr. Victor Horsley. As first an assistant to Prof. Burdon Sanderson, he acquired that familiarity with the endurance of living tissues, and the minute functions of the various organs, which has enabled him to make his operations upon the human patient the marvel and the admiration of contemporary surgeons. So with the leader of the

Austrian surgeons, Billroth, and notably with his best known pupils, like Czerny, Gussenbauer, Wölfler and others. So too in the highest degree with that great Lyons master of bone-surgery, Ollier, whose volumes bristle with facts attesting his devotion to the experimental method.

Among living surgeon-histologists no names better deserve mention perhaps than those of Paget, of Lannelongue and Butlin. Volkmann led here, as he did in every other department, and, though now he rests from his labors, is entitled to be named with the others who were his contemporaries.

Of surgeon bacteriologists perhaps the best known are Rosenbach and Fehleisen, though Cheyne and Neisser, with others equally deserving, are scarcely less known.

Nor must we forget what home surgeons are doing in these various fields, for such names as those of Parkes, Senn, Halstead and Warren must be written in large letters on this particular tablet of surgical history.

Pathology, then, is a *sine qua non* for the modern surgeon, and everything which fosters fondness for, and familiarity with, it should meet with hearty encouragement. To this end it must assume an ever-increasing importance in every college curriculum, and to this end also every such collection as the invaluable one which this college contains should be daily haunted, and no opportunity of securing and preparing specimens for private or public collections should be neglected. Above all things, the many opportunities for study of comparative pathology, both natural and experimental, which are constantly afforded, both in city and country, should be utilized to the fullest possible extent.

The most brilliant illustration of what such study may do for one is afforded in the person of Mr. J. Bland Sutton, who stands to-day a young man, yet one of the most prominent figures, in my estimation, among pathologists, living or dead; who has made thousands of autopsies upon animals, the number including nearly every known genus, who has contributed to the magnificent collection of the Royal College of Surgeons some of its most valuable specimens, and who in tastes and acquirements well deserves to be considered the legitimate successor of John Hunter. He, practising and now working

as a surgeon, has, nevertheless, almost created the science of comparative pathology; and it is to be earnestly hoped that he may be induced to undertake a systematic treatise upon this subject—which as yet does not exist in any language. Of the value—surgical and pathological—of his writings, only those can speak who have read them, as all ought to have done. I think he will pardon me if I place his career before you as one which is deserving alike of greatest praise and closest possible imitation.

To this end, also, the founder of this course of lectures, with that wisdom and foresight for which he was so distinguished, ordained that they should be devoted to topics connected with surgical pathology. Although the field is immense, the number of laborers in it is correspondingly large, and it has been my aim less to intrude upon you personal views and experiences, or statements of personal work, than to collate and compare the results of investigators the world over, and to invite your attention to the present state of knowledge concerning some of the most contested or most important and interesting topics to-day discussed or considered by the surgical profession.

I have in my library an interleaved copy of a "Syllabus of the Course of Lectures on the Principles and Practice of Surgery, Delivered in the Jefferson Medical College," by Thomas D. Mütter, M.D., published in 1847, with copious notes, interlineations and annotations by Prof. Howard Rand. I have been much interested in looking over the note headings to see the extent of its author's erudition in the surgical pathology of his day, and the attention which he compelled his students to devote to it, and have often thought how well it would be if some of the surgical teachers of to-day would more closely imitate him in this respect. To be sure, there is much therein which needs elision, revision or contradiction, such as the statement on page 10, that suppuration can occur in 35 minutes; yet the whole syllabus so clearly indicates the character of his teaching and his bent of thought, that one scarcely wonders at the general drift which he so wisely insisted this course of lectures should assume.

Inasmuch, therefore, as all pathological processes begin

with alteration of nutrition, of cell activity and of the constitution of the vital fluids, it has seemed wise to first discuss a few of the more important of these changes in the light of recent studies; in other words, to begin in our studies of surgical disease where nature appears to begin in its production.

The inflammatory process is modified according to conditions of environment and cause, and may be classified under four different headings—as regenerative, productive, exudative and destructive. The *regenerative* form especially concerns the surgeon in the matter of healing of wounds. It is always followed in every case, and in whatever disease, by cicatrization. *Productive* inflammation is met with after injuries or destruction of particular tissues; is at times adhesive, at times hyperplastic. *Exudative* inflammation is serous, sero-fibrinous and sero-hæmorrhagic. *Destructive* inflammation is either suppurative or gangrenous, or both. To these four forms might perhaps be added a fifth, the *granulomatous* inflammation, of which we shall later speak more at length.

To the serous form of exudative inflammation there has been given the name of inflammatory œdema. This must be sharply distinguished from those forms of œdema which are due to mechanical disturbances of the circulation. When the blood stream is interfered with in the veins, while the arterial stream is circulating in full force, there must occur stasis in the capillary veins. Under these circumstances serum is forced through the distended vessels and into the tissues, and there fills the intercellular spaces and minute canals. This form of œdema is as different from inflammatory as is blood serum from blood. In the mechanical form the serum is poor in fibrin, while in the inflammatory form it contains not only fibrin, but the other elements of the blood. Serous inflammations of higher grade which contain a relatively large percentage of fibrin are known as sero-fibrinous. The flocculent precipitate of fibrin is produced by a mutual reaction of fibrinogin and fibrino-plastin, just as they produce blood clot under other circumstances. In rare cases there is added to the exudate of serous inflammation the red blood corpuscle element. When this is in excess it is known sometimes as hæmorrhage by diapedesis. The ordinary termination of exudative inflamma-

tion is a complete return to the normal standard. In a small proportion of cases, especially involving serous cavities, there remains a portion of the exudate, which predisposes the part to a recurrence of the trouble.

Rapid progressive inflammation leads not infrequently to stasis and to coagulation of the blood in surrounding tissues or in the smaller arteries. If now the collateral circulation is sufficient resorption is still possible; if not, local gangrene is the result. Around the margin of such a gangrenous focus there will always be a zone of suppuration which may be taken as an instance of *pyo-gangrenous* inflammation. It is not necessary to have inflammation of the highest grade in order to produce gangrene; it is frequently enough to have the supply of nutritive material shut off. Thus one sees often, even in a simple case of this kind, considerable portions of tendon slough off, since the tendon contains no blood vessels, but only canals through which nutrition is furnished by osmosis. Should such an inflammation progress to the neighboring muscles, it loses its gangrenous character in all probability, since here blood vessels supply the proper nourishment. For gangrene of muscles ordinarily, the highest grade of diphtheritic inflammation is necessary.

Granulomatous inflammations.—These are always chronic processes. One sees them confined almost to individuals of peculiar constitutional condition, such as are usually grouped under the head of the scrofulous, the syphilitic or the leprous. In contra-distinction to the serous and purulent forms of inflammation, these have little or nothing to do with skin lesions or access of air to the tissues. They are produced rather without injuries, and in those cases in which injury is alleged, it is usually of the nature of a deeper crushing without cutaneous lesion. Most of these cases pertain to the period of youth. Most commonly the bone marrow is involved, and it seems as if the marrow of growing bone were peculiarly liable to this affection. Still, granulomatous inflammation of the skin is common, as well as in joint cavities. If we examine a piece of tissue from the beginning of a granulomatous inflammation macroscopically and microscopically, and compare it with a small fragment from a case of purulent inflammation,

we shall not find any marked difference; both consist of new blood vessels with heaps of small round cells between them. In their further course,however, the difference notably increases. The granulation tissue in the neighborhood of the acute abscess is a great help to its subsequent healing. In the other case, however, the cells break down after infection, and form small abscesses which frequently coalesce, and these form others of considerable size, which pursue the well known course of the sub-acute or cold forms. As the result of spontaneous perforation of these latter we have granulating ulcers and fistulous passages of an ulcerative character, which may lead deeply, even down to the bone marrow. The significant feature of granulomatous inflammation is, that it never tends to formation of a firm cicatrix or healing; it tends to remain indolent, or to become more and more destructive. Its destructive products are never natural pus; they contain fragments which have a caseous appearance, and they lead to so-called caseous degeneration, or, through fatty degeneration, we may meet with veritable fat balls in its substance. There occurs a complete transformation of albuminoid, nitrogenous substances, into those which are fatty and free from nitrogen.

Any synopsis of the forms of inflammation leads by a path which cannot be avoided to the topic of thrombi and thrombosis, and indeed the question of the formation of thrombi is one of such universal interest, since thrombi have so much to do with surgical diseases, that it will be well to stop to consider briefly how, and under what circumstances, they are most often formed. The first variety of which we shall speak, following Klebs, is the coagulation of fibrinous form, the second that which is formed from red cells and globulin; the third that from leucocytes; yet another is formed from hæmatocytes, and a fifth is produced through the instrumentality of the hæmatoblasts, or the third corpuscular element of the blood. Each of these forms may be met with by itself, but mainly we have to deal with mixed thrombi.

A. *Fibrinous thrombi.*—Fibrin is the principal material out of which these are formed, and this possesses the property of adhering to the vascular wall, which naturally appears to be the first requisite of thrombus formation. This is the form

which most commonly gives rise to secondary thrombosis or embolism. The cases in which a simple separation of fibrin from the circulating blood occurs by itself are rare; some foreign body in the circulation is usually the prime cause. A roughness of vascular surface has been supposed to be sufficient to favor coagulation of the fibrin, but the condition of atheroma of the vessels, by which their interior is roughened, does not lead to thrombosis as often as would be expected. The death of the vascular wall, whose life is an important cause of the fluidity of the blood, does not invariably lead to thrombosis, as the uncovered calcareous plates of the interior of the vessels will prove. Even cauterization of limited areas of vessel walls does not necessarily always produce thrombosis; neither does ligature of vessels. On the other hand when fibrin ferment is introduced into the circulation, or when the same is set free in the blood, as may be done by injections of ether, we have most extensive thrombus formation. This naturally raises the question whether such a thing can occur under natural conditions, and this has hardly yet been answered definitely. The thrombi which form in the heart during the last moments of life can hardly be considered to have formed under natural conditions. There is considerable reason to think that in septic conditions the fibrin ferment of the patient's blood is altered in amount or activity.

B. *Hæmatoblastic or globulin thrombi.*—The third corpuscular element of the blood is now well known, although whether it be a normal constituent, or an intermediate or retrograde form, is hardly yet decided. Without discussing to any extent the conditions under which thrombi are produced by the action of these corpuscles, we have to side either with those who consider them to be normal blood elements, and recognize under what pathological or physiological conditions they increase, or else we must deny that they are normally present. Hayem found a significant increase after ingestion of food, but in pathological conditions different observers have obtained so widely varying results that it is impossible, as yet, to assign to them any distinct role. Here, again, we must allude to the fact that the cauterization of areas of vascular walls does not necessarily lead to thrombosis, with the exception of those

points at which a loosening of the cauterized scale leads to some unevenness of the surface. Even at these points it does not always occur. Evidently then when thrombosis does here occur, some condition not obtaining in the vessel wall itself must lead to it. Perhaps the rapidity of the blood stream has much to do with it; but more important, probably, is the part played by this third corpuscular element. It has hitherto been very difficult to experiment with this, since the conditions of the experiment inevitably lead to inflammation of the areas under observation. However, Lowit has recently succeeded in examining the mesentery of mice under castor oil, by which no inflammation is produced, and by means of which he was able to convince himself of the absence of hæmatoblasts at points where the circulation was slackened. Slight cauterizations of the vessels with points of nitrate of silver produced hæmatoblastic thrombi, which contained leucocytes, and which broke loose and were rapidly reformed at the same points; and he was even able to observe the breaking down or disintegration of the stagnant, red corpuscles. The leucocytes also broke up, after a time, as Zahn has already described.

C. *White or leucocyte thrombi.*—These were long ago recognized by Virchow as a separation of the white corpuscles, which earlier authors had held to be pus corpuscles, taking place where a slowing of the circulation leads to thrombosis. In such cases, as Cohnheim showed, the white corpuscles leave the more rapid central stream, and attach themselves to the surface of the vessel wall, especially at those points where circumstances favor, as the point of division of the vessel, or where a sudden curve or dilatation leads to stagnation of the current. Other favoring circumstances are changes in the intima, such as roughening or minute alterations of the endothelium by which exudation is more easily permitted. Thrombi formed by leucocytes alone are relatively rare, a leucocyte immigration into a fibrinous thrombus naturally being included under this term. They are most common in cases of leucæmia in which the capillaries of the mucous membranes, especially of the intestines and nose, are filled with them and made to resemble white streaks. They occur also in the rear of some emboli when the section of the occluded vessel behind them is very short;

also behind venous valves and in the spaces between the bundles of muscle fibres in the heart, and in the sheltered cavities which form in connection with aneurisms and varices. They may also form in slowly circulating blood as free thrombi.

D. *Red blood corpuscle or hæmatocyte thrombi.*—Constituted primarily from adhesion of the red corpuscles. This is a genuine stagnation form. Aside from stagnation, a second condition, namely the removal of the blood plasma from the stagnant blood mass, is a contributing feature. It takes place also when pressure is exercised upon the red corpuscles. White corpuscles which are entangled with the red are usually destroyed or lose their identity. The pure stagnation thrombi are usually formed at those points where a good-sized vascular area is shut out, as for example, after the ligature of a vein of some size. Under these circumstances the arteries are dilated and the collateral circulation easily takes off the overflow. All so-called ischæmic conditions, depending upon arterial contraction, can cause stagnation thrombi if they occur in a region whose veins are enlarged and filled with plenty of blood. The essential condition of the stagnation thrombus, the lessening of venous flow, is always accompanied by an increase of pressure in the capillaries and veins, and it is this which determines an increase of exudation, and this in turn leads to a typical œdema. General or partial venous stasis furnishes all the necessary requirements for the formation of hæmatocyte thrombi. Very typical forms of these are met with in senile gangrene; so also contusions and inflammations of injured portions produce the same effect. Especially unfavorable is the extension of inflammatory processes along the arteries, by which are produced extensions of thrombi, mostly in the shape of fibrinous additions. A marked instance of these thrombi is met with often in the so-called arterio-venous aneurism, that is, the traumatic communication between an artery and a vein. There belong also in this category a large number of divers forms resulting from venous stasis combined with hæmorrhage, such, for instance, as occur about the constriction in a case of strangulated hernia. Such conditions lead frequently to so-called hæmorrhagic gangrene. So far as the future of these

thrombi is concerned it is not necessarily unfavorable so long as further changes in an undesirable direction do not occur, since with improvement of the circulation compensatory and absorbtive processes are instituted; but if they exist too long there occur changes in the character of organization, or, if infected, in a destructive direction.

E. *The mixed or the thrombus in layers.*—These layers, as is well known, are formed by deposition at different times of the solid material of the blood, this material being now of one of the above forms, at other times of another. The surgeon meets with this variety most commonly in dealing with aneurisms or hæmatomata, in which concentric deposits from contained fluid have taken place. In another signification the mixed forms are met with often in those thrombi which obliterate vessels.

As appears above, explanation of some of these forms of thrombus-formation is simple, at other times it is difficult, or as yet impossible. Remembering how rapidly blood coagulates outside the body, remembering, too, what differences may be observed, in this respect, in the blood of different patients, it will be seen that it can scarcely be expected of us to imitate outside of the living body the conditions existing within it, nor to solve all the problems of vital chemistry.

Nevertheless, a distinct advance has been made, first in the ecognition, and then the accurate study of ptomaines and leucomaines, and there is now every reason to think—nay, to state with little or no reserve, that there often takes place a form of ptomaine or leucomaine intoxication, analogous to that produced experimentally by certain substances, such as the fibrin ferment; and that under these circumstances there may occur an almost instantaneous and extensive thrombosis, or analogous change, wherever the poison reaches. Surely in this way are we to account for the altered quality of the blood so universally recognized and commented on as among the changes during and after death from the various infectious diseases. So large a part in the pathology of the blood is now borne by these alkaloid substances and toxines that to them we must presently devote some attention.

But, dealing still with the blood and its natural constituents,

for a few moments, let us see what recent research has shown us concerning blood loss, and how it is atoned for.

In cases of traumatic anæmia there is a relative or rather an absolute *decrease* of leucocytes. Ehrlich has shown that 80% of white corpuscles are formed from lymphocytes, while the balance are represented by multinuclear neutrophile, or mononuclear neutrophile cells and transition forms, in the proportion of 14, 3, and 3%. His eosinophile cells are formed solely and normally from bone marrow. The decrease in number of leucocytes in traumatic anæmia is due to failure of equilibrium between the true lymphatic structures on the one hand and the spurious, like the spleen and the bone marrow, on the other. Cohnheim some time since showed how in cases of acute anæmia following injury the bone marrow tends to revert to the embryonic condition, and its failure to produce these cells may, perhaps, be explained in this way. They constitute a definite constituent of normal blood, and are found in proportion of 2 to 4%, which may even increase to 10%. Their complete absence, therefore, points to a disturbance of function, at least in bone marrow.

As a matter of common interest we may add here that the character of a given case of anæmia may be largely determined by a study of the red corpuscles. In all severe forms nucleated red cells are found, which bespeak an active regenerative process. In secondary anæmias these nucleated corpuscles have normal size, and may be called normo-blasts; while in the pernicious forms they have a much larger size, corresponding to embryonal types, and may be called giganto blasts. This method of differential diagnosis is, indeed, recommended by Ehrlich as the safest of all.[1] Possibly this fact also finds its explanation in the above-mentioned discovery of Cohnheim.

Hæmoglobin. That the amount of hæmoglobin in the blood varies within wide limits under different conditions has been known for some time, yet it is only recently that a careful

[1] By far the best method of examining these various blood-cells is that known as Ehrlich's double-staining, the aniline dyes employed consisting of acid fuchsin, methyl green and orange green.

study of the amount present in various surgical diseases has been determined. At the Congress of German Surgeons of 1890, Mikulicz presented the results of a study of some 400 cases, mostly operative. Two questions especially concerned him. First, in what time after serious loss of blood in man does regeneration occur, and what influences thereupon have age and sex; second, in relation to those diseases which we are inclined to associate with a vitiated constitution, what striking variations have we in the amount of hæmoglobin in the blood, and its regeneration after hæmorrhage? The first question has been studied in animals from many sides, but only a few observations have been made in man. Concerning the second question, Leichtenstern and Laker have offered some interesting observations, but only in relation to tuberculosis. Mikulicz perceived during the examinatson that the estimation of the actual blood loss depended on manifold factors. In the case of each disease the amount of hæmoglobin had been determined before the operation as well as afterward at stated intervals, say at two or three days. The amount of the loss of blood found expression in the percentage determined from the original amount of hæmoglobin in the blood, while the gradual increase of the latter explains the augmented blood regeneration.

The estimation of the hæmoglobin was made by Fleischl's hæmometer. This instrument is easily handled, and permits an estimation in from three to five minutes. Personal equation produces error of from 2% to 5%. The subjoined table gives a summary of the amount of hæmoglobin and of blood regeneration, that is restoration to previous or normal standard, with reference to sex and age. It was made up from observation of one hundred and seventy-five patients who presented no so-called constitutional disease.

The ideal normal standard of 100% was discovered with Fleischl's instrument only in a few individual instances of strong young men in the third decade of life. The general average is considerably lower, the highest average appeared in men in the third decade of life, viz., 92%. This may be partly explained by the fact that persons presenting at a public clinic are scarcely to be considered as highest types of their class.

The female sex shows a smaller amount of hæmoglobin in the blood than the male. The different averages given here—about agree with the tables of Sterling, viz., males, 87.8, females, 84.5.

TABLE 1.—THE AMOUNT OF HÆMOGLOBIN AND BLOOD REGENERATION WITH RESPECT TO AGE AND SEX.

Age.	Amount of Hæmoglobin.			Blood Regeneration.		
	Males and Females.	*Males.*	*Females.*	*Males and Females*	*Males.*	*Females.*
	Per cent.	Per cent.	Per cent.	Days.	Days.	Days.
1–10 years.....	73.8	74	73	22.4	20	25.5
10–20 years	82	83	81	17	15	18.5
20–30 years.....	88.7	92	80.7	11.6	10.6	17.7
30–40 years.....	84	88	76.6	12.5	11	14
40–50 years..	82	84	78	18	14	2
50–60 years.....	84.8	88.6	79	20.6	18	24
60 and above.....	83	85	78	25	24.5	29
Average.....	81.6	83	78	17	15.6	20.4

Sterling's examinations were made with Gower's instrument which gives a higher value than does that of Fleischl. Some striking differences appeared in reference to the speed of regeneration of lost hæmoglobin. The most rapid occurs in the third or fourth decades of life, it being much lower with children and the aged. This corresponds with the clinical experience that the very young or old bear loss of blood more poorly than do those of middle age. It also appears that females are considerably behind males in the same respects. With women in the third decade of life the average time of regeneration of 14.7 days agrees well with the observations on puerperal patients by Meyer, who observed within 14 days a permanent and complete restoration of the normal standard. The amount of blood lost also influences the result. Blood-

loss which was indicated by 15% loss of hæmoglobin was, on the average, atoned for in 14 days, by 20% blood loss in 20 days, by 25% blood loss in 21 days, and all proportions over 25% of blood loss required on an average 29 days for restoration.

The minimum proportion of hæmoglobin reappears first after several days, quite in conformity with observations on animals. The greater the amount of blood lost, the later appears this minimum. When the blood-loss is up to 15%, this time is three and one-half days; with blood losses over 25% it averages nearly ten. The greatest loss of hæmoglobin appeared in a woman who had undergone extirpation from the abdominal wall of a large fibroma weighing some 30 pounds. Her proportion of hæmoglobin sank from 70% to 22%.

Regarding the largest losses of blood which men can stand, these appear to depend less upon actual loss of hæmoglobin than upon how much hæmoglobin still remains in the body. The minimum amount in a single patient after a major operation amounted to about 20%. In three cases dying of collapse this amount sank to about 15%.

Mikulicz believes that many of the cases dying on the second or third day after severe operation from so-called collapse are to be attributed to oligo-chromæmia, *i. e.*, deficiency of hæmoglobin in the blood. It is quite possible that an expert in these examinations might, from an estimation of hæmoglobin, give a reliable judgment as to whether in a given case the patient could or could not withstand a severe operation. In eleven cases estimations were undertaken just before and just after operating, in order to determine the effect of mental emotion, narcosis, etc. In every case there was found a loss of from 5% to 10%, from which it is easy to decide that chloroform narcosis exerts a decided influence upon the blood.

Table II gives a review of the amount of hæmoglobin and the regeneration period with different diseases which exercise more or less vital disturbance or which stand in causal relation with cachexia or dyscrasia. In seventy-nine cases of local tuberculosis where the hæmoglobin averaged 63% as against 81.6% normal, the period of regeneration was delayed at least a week. Delay was most conspicuous in cases of tubercular

diseases of the lower extremities, least so with those of the soft parts. It is likely that every such lesion by which functional disturbances and impaired nutrition are caused must in-

TABLE II.—THE AMOUNT OF HÆMOGLOBIN AND THE BLOOD REGENERATED WITH RESPECT TO CONSTITUTION.

Cases	Disease.	Amount of Hæmoglobin before Operating.	Blood loss in per cent. of the Hæmoglobin Reduction.	Regeneration.
		Per cent.	Per cent.	Days.
1	Healthy.....	81.6	15.5	17
2	Tuberculosis:			
	a. Altogether.....	63	14.7	24
	b. Bone.....	....	15.5	....
	Lower extremity.....	60	15 5	26
	Soft parts	70	13	17
3	Actinomycosis,.....	46	....	....
4	Syphilis, tertiary.	55.4	15.4	18
5	Benign tumors:			
	a. Altogether.....	79	17.4	18.8
	b. Without complication.	83	15	16.8
	c. With rapid growth or of considerable size...	70	23.8	24.6
	d. With functional disturbances or putrefaction.	67.5	14.6	16.6
6	Malignant tumors:			
	a. Altogether.....	60	17.2	26
	b. Without complication.	68.5	15.5	23
	c. With rapid growth or of considerable size...	56.6	18.2	27.8
	d. With functional disturbances or putrefaction.	57.6	17.8	27

fluence the condition of the blood. Laker also obtained similar results. The question whether tuberculosis as such influences the amount of hæmoglobin in the blood, or whether the

descendant of a family characterized by a minimum of hæmoglobin is thereby predisposed to tuberculosis, cannot yet be answered from data at hand; but it is hardly likely. Certainly Mikulicz found that, in a series of cases, after complete healing of local tubercular trouble the amount of hæmoglobin rose far above the original height. On the contrary, in several cases in which the disease could be only incompletely removed, or where relapse occurred, the proportion of hæmoglobin did not attain the original height.

In ten patients with tertiary syphilis the amount was considerably reduced, though the regeneration period was uninterfered with. In four severe cases of actinomycosis the amount was still smaller. Finally, in thirty-two cases of benign, and seventy-two cases of malignant tumors, divided into three categories, *a*, uncomplicated tumors; *b*, those of rapid growth, of considerable size, or of severe hæmorrhages; *c*, those which were breaking down, or causing severe functional disturbances, as pressure upon the trachea or alimentary canal, the average amount of hæmoglobin in the benign tumors was reduced but very little from the normal; while in the first group the average was even higher than the normal, and in the second and third it was more or less reduced. The most striking reduction was in a case of large goitre causing severe compression of the trachea. In malignant tumors the average is reduced to about 60%. The statistics of Mikulicz concerning cases of mammary cancer, agree with those of Schmidt, of Heidelberg, who estimated it at from 50% to 60%. In malignant cases also the period of complete regeneration is materially retarded. Furthermore it was found that incomplete removal or recurrence prevented a typical regeneration or restoration to the proportion present before the operation, while after successful radical removal complete restoration to the previous standard was obtained, with sometimes positive gain. A woman who had gained thirty pounds after resection of a cancerous pylorus, showed after three months hæmoglobin to the amount of 65%. It would appear, therefore, as if some prognostic significance might be attached to an accurate estimation of hæmoglobin at intervals after removal of malignant tumors.

Everywhere, and until recently by all, the animal organism has been supposed to be one which could not live without air. It may well be one of the proud boasts of this present generation that it has shown that life of a complex organism is made up of the life of its component parts, mainly animal cells, and that, as Gautier has shown, at least one-fifth of it is *anærobic*. In other words, not all vital force comes from combustion, nor from the *ærobic* life of cells. But whether they need or eschew oxygen, the cells excrete products which must be expelled from the organization, else would the animal quickly succumb, were the carbonic dioxide, the urea, the water, or even the heat, which it produces, allowed to accumulate within itself. The products of ærobic life are poisonous and inimical enough, but those of its anærobic vitality are peculiarly so. They are of the same character as those which result from all bacterial activity, toxic, and for the most part, alkaloidal. Those of this class, constantly present in prolonged or violent putrefactive changes, belong to the pyridic and hydropyridic series, differing little from the bases of hemlock and tobacco; and even more powerfully poisonous substances are met with under similar conditions, such as muscarine. Since, then, we live anærobically, in part, we may expect to find such analogous substances as may result from the splitting up of albumenoid bodies, and these are the leucomaines. Let me here quote Gautier verbatim:

"The products of life, ærobic and anærobic, can not be retained within the organism for any length of time with impunity; normally, they undergo destruction and excretion by economic processes which are constantly in operation. But if from any cause the functional play is interrupted, should there be emotional disturbance of the nervous centres; should sudden chills suppress the action of the skin, or insufficient æration take place; or, if, finally, from any less obvious cause, leucomaine products be more abundantly formed within the cells, or be so defectively absorbed, excreted or oxidized as that the blood becomes charged with them, they are carried to the nervous centres, which regulate the central life and function as a whole; immediately disorder becomes general, complete, and necessarily assumes progressive forms —in a word, disease de-

clares itself and undergoes development."—(Preface to Brown's "Animal Alkaloids.")

Like our proper cells ferments or specific microbes live—some of them—anærobically, as those of tetanus, malignant œdema, and some forms of septicæmia; while others live ærobically, like those of anthrax, pneumonia, etc. Others yet possess facultative powers in both directions, like tubercle bacilli. But each and every one *must* excrete, and ptomaines and leucomaines, like carbonic dioxide and urea, are the residual products of life, solid, liquid or gaseous, effete and pernicious, which may become the cause of disease, or may accompany it and mask the prime cause; and such they are, whether arising from the normal cells of the organism from within, or in the microbic cell introduced from without. Once set free within the system our tissues make no fine distinctions of origin or intended destination, but suffer in proportion to dosage of poison and susceptibility thereto.

We shall have to recur to this subject when dealing with the matter of surgical sepsis, so can afford to dismiss this aspect of it here, delaying only for the sake of definition and classification.

To follow all the chemical changes which the complex tissue molecule may undergo would be too foreign to our intent this evening. Yet it is not enough to merely say that a ptomaine is the alkaloidal waste product of a cell; it is in reality much more than this, since it represents the final production of a series of cyclical changes which represent tremendous cellular activity. Brown sums up the idea tersely when he says:

"A ptomaine thus presents itself as the residual skeleton, as it were, of the proteid molecule, which has undergone continuous disintegrative action, the ultimate terms of which are represented by the pyridic bases; so that, considered from a purely chemical point of view, a ptomaine may be defined as the cyclical nucleus of a proteid molecule, that has undergone complete destruction in the process of putrefaction."

The essential idea conveyed in the term is, then, that of *putrefactive* change, *i. e.*, one begun by cells introduced from without, and having no place in the healthy body, when everything is working smoothly.

On the other hand, it has been amply shown, not alone by Gautier, that the important chemical function of all animal tissue is the incessant elaboration of alkaloidal products formed at the expense of proteid material, just as carbonic dioxide and urea are simultaneously formed. Upon these vital and essential alkaloids, Gautier conferred the name leucomaines, which term he limits to those derived from albuminoid substance and formed in the living organism and before its death. It does not necessarily follow from this that the same base may not appear at one time as ptomaine, at another as a leucomaine, though this must occur comparatively seldom.

It will prove germane to our subject if we pause here to give a list of these alkaloids and bases, as well as to speak of a few other substances which, for lack of a better category in which to place them, we may call toxines.

Schwalbe, following a convenient and recognized system, has classified ptomaines and leucomaines as follows (*Deutsche Med. Woch.*, 1890, No. 36):

A. Ptomaines free from oxygen, whose bacteria are not yet known.—These persist throughout putrefactive activity.

Collidin ($C^8H^{11}N$). Isolated by Nencki, and regarded by him as isophenylethylamin. Appears to be formed only by a mixture of gelatin and hog's pancreas.

Pawolin ($C^9H^{13}N$). Separated from putrefying mackarel by Gautier and Etard.

Hydrocollidin ($C^8H^{15}N$). From the same; 7 mgr. kill a bird, with tetanic cramps.

Dihydrocollidin. Discovered by Cahours and Etard; made by treating nicotin with selenium

Neuridin ($C^5H^{14}N^2$). Found by Brieger in numerous rotting substances. Appears in putrefying human flesh in 3 days, increases to the 15th day, and then disappears. When absolutely pure is not toxic.

Cadaverin ($C^5H^{16}N^2$). Appears after 3 days in putrefying human flesh. Bocklisch found it in herring-brine, and in cultures of the Finkler-Prior bacillus. Dissolved in methyl alcohol it forms with iodide of methyl dimethylcadaverin. Is not toxic (according to Behring) in large doses. Causes inflammation and coagulation-necrosis (Scheurlen, Grawitz).

Putrescin ($C^4H^{12}N^2$). Found by Brieger in cadavers after the 4th day; also by Bocklisch in herring-brine. Effects like those of cadaverin.

Saprin. Discovered by Brieger. Quite similar to cadaverin. Not toxic.

Mydalein. According to Brieger this appears in cadavers after the 7th day. Is quite toxic. A few milligrams injected beneath the skin of a rabbit produce copious secretions from the nose, mouth, lachrymal and intestinal glands, as well as dilatation of pupils and vessels, and rise of temperature, with final somnolence; 5 mgr. kill a cat.

Several other more or less toxic alkaloids, to which names have not yet been given by their discoverer, Brieger. One of these causes violent diarrhœa and peristaltic motion.

B. Ptomaines containing oxygen, whose bacteria are unknown, are connecting links between ptomaines and leucomaines met with alike in dead and living tissue.

Neurin ($C^5H^{12}N)(OH$). Previously known in nerve tissue, but found also by Brieger in cadavers. Is very toxic; 4 mgr. kill a rabbit, causing severe peristalsis, profuse sweating, contraction of pupil and of spleen, and tetanic cramp. Is antagonized by atropin.

Cholin ($C^5H^{15}NO^2$). Extracted by Stricker from bile. Is really both a leucomaine and a ptomaine. Is toxic in the same way as neurin, but much less so.

Muscarin ($C^5H^{13}NO^2$). First discovered in mushrooms by Schmiedeberg; later found by Brieger in putrefying dorse or torsk (fish). Has been synthetically produced by oxydizing cholin with nitric acid. Is antidoted by atropin.

Gadinin ($C^7H^{16}NO^2$). Also extracted by Brieger from rotting torsk.

Two unnamed ptomaines, isolated by Pouchet, from the sewerage of manufactories where animal tissues are utilized.

Mydatoxin. Found by Brieger in putrefying human intestines and horseflesh. Slightly toxic.

Mydin. Same as above. Has marked reducing powers. Not toxic.

Methylguanadin. From rotting horseflesh. Is toxic and produces tetanic spasms.

Another unnamed ptomaine, found by Brieger in the same material, has powers similar to those of curare.

Mytilotoxin ($C^6H^{15}NO^2$). Isolated from the flesh of the limpet. Along with it Brieger found betain or oxycholin, which is not toxic; also a base which has marked sialogogue properties.

Peptotoxin. Discovered by Brieger in peptone, and found to have curarizing properties.

C. Ptomaines isolated only from pure cultures of known species of bacteria.—For these we are mainly indebted to Brieger, who also cultivated most of the organisms in media made with human flesh, in order to imitate our body chemistry as nearly as possible.

Typhotoxin. From cultures of typhoid bacilli.

Tetanin. From cultures of tetanus bacilli. Very toxic; producing first lethargy and apathy, then tonic and clonic spasms and death. Lately it is claimed that this has been extracted from the muscles of a patient with tetanus.

Tetanotoxin. Distilled from alkaline cultures of the above. Is weaker than tetanin, nevertheless strongly toxic.

Spasmotoxin. From same source, with similar properties.

A fourth toxic substance from this source produces also spasms, but especially causes copious secretion of tears and saliva. None of these four appear in the urine.

From cultures of the cholera spirillum *six* bases have been isolated—methylguanadin (*supra*), cholin, cadaverin, putrescin and two unnamed alkaloids.

To these I would add another class of

D. Ptomaines produced by certain species of bacteria, though as yet not necessarily identified solely with such species.

Tyrotoxicon, if produced exclusively outside the living organism.

Ammonia.

Trimelhylamine $(CH_3)_3N$. Both produced by staphylococci growing on beef or veal; the latter produced especially by the s. albus, by micrococcus prodigiosus and by streptococcus pyogenes. Both these are irritating, the former particularly in its nascent state. The latter if not strictly a ptomaine is a descendant of one or closely allied to one, and at all events is injurious in the same way.

Toxalbumens.

Save that they are not, strictly speaking, ptomaines, these bodies are produced in the same way (by bacterial action) and produce disturbance in analogous manner.

A toxalbumen has been isolated by Brieger and Fraenkel (*Berl. klin. Woch*, 1890, Nos. 11 and 12) from cultures of Lœffler's diphtheria bacillus, which is an amorphous white powder, possessing fatal activities in small doses.

Other toxalbumens have been found by the same workers in cultures of the microbes of cholera, tetanus, typhoid, anthrax and of suppuration.

Leucomaines are alkaloidal substances produced during the life of the individual within his organs and tissues, by which they are entitled to rank as a class alongside of ptomaines. Their existence was first predicated by Gautier on purely theoretic or inductive grounds, which he then demonstrated to be correct by the discovery of a number of these substances. Roussy and Hugouneng first grouped them, about, as follows:

A. Betain-leucomaines.

Betain or oxyneurin ($C^5H^{11}NO^2$). First found by Scheibler in the red-beet. Liebreich found it in human urine and produced it synthetically by his different processes. Brieger found it in limpet's flesh. It appears to be identical with trimethyl glycocoll. Is not toxic.

B. Leucomaines of the uric-acid group.

Carnin ($C^7H^8N^4O^3$). Found in meat extract and brewer's yeast water.

Adenin ($C_5H_5N_5$). Met with in pancreas and spleen. With potassium hydrate forms water and "cyankali"

Guanin ($C^5H^5N^5O$). Common in both animal and vegetable world. Kerner found that the excretion of urea was proportional to the amount of it which he administered to rabbits.

Sarcin ($C^5H^4N^4O$). Found in living flesh. Isomeric and nearly identical with crystalline white powder.

Hypoxanthin.

Xanthin ($C_5H_4N_4O_2$). First found by Marcet in vesical calculi; then recognized in many organs.

Pseudoxanthin ($C^4H^5N^5O$). From muscles of swine.

C. Creatinin-leucomaines.

Creatinin $C^4H^7N^3O$). First produced by Liebig by treating creatin with hydrochloric acid; then recognized in urine. Has caustic properties. Ranke states that when introduced into the circulation it increases the irritability of peripheral nerves and produces muscle contractions.

Xantho creatinin ($C^5H^{10}N^4O$). Produces in small doses apathy, somnolence and nausea.

Cruso creatinin ($C^5H^8N^4O$). Resembles creatinin.

Amphi creatinin ($C^9H^{19}N^7O^4$). Same.

Two others isolated by Gautier, but not yet sufficiently studied.

D. Leucomaines of special secretions.

Viperin. *Echidnin.* *Salamandrin.* *Cobraïn.* *Crotalin.* *Najin.* *Elaphin.* *Cedrin.* *Valdivin.*	Poisonous secretions of reptiles and serpents. Their poisonous activities seem to be mitigated by the addition of potassium hydrate or sodium carbonate.

According to Calmels the primarily active agent in all of these albuminoid secretions is *methylcarbylamin*, which he believes to be produced in the cells of the gland in a nascent condition by the action of formic acid upon glycocoll. This methylcarbylamin seems to have frightfully poisonous properties, inhalations of it killing rabbits in a few seconds. Schwalbe also states that equally poisonous substances are secreted by certain fish in Chinese and Australian waters.

Protamin. Discovered by Miescher in semen.

Spermin. From same source.

E. Leucomaines from particular organs.

The eyes contain *neurin*, the brain *neurin* and *cholin*, the heart, lungs and blood the former. In fresh veal Guareschi and Mosso *methylhydantoin*. Wartz examined expired air and there found two bases, *ammonia* and another gaseous alkaloid not yet named. Brown-Sequard and Arsonval have also discovered a gaseous base in expired air, which produces in rabbits a lowering of respiration rate and an exaltation of pulse, contraction of the pupil, and fatal diarrhœa with colic. From the fresh spleens of swine Morelle extracted two bases, one of which kills frogs in five hours after complete paralysis of sensation. In urine a new base has been discovered by Pouchet. Bouchard has shown how those diseases which accompany or are caused by increase of putrefaction in the alimentary canal are characterized also by a greater excretion of leucomaines with the urine.

F. Leucomaines which are produced in the bodies of patients and of diseased animals

Pyocyanin belongs in more than one of these sections. Has been isolated from pure cultures of bacillus pyocyaneus, as well as from pus, blue sweat, etc. In contact with oxygen it changes to *pyoxanthose.*

Cadaverin and *putrescin* have been found in the urine and fæces of patients suffering from cystinuria; consequently we must probably consider cystinuria as due to intestinal mycosis.

Spermin, discovered by Schreiner in human semen, has been found in cultures of the cholera spirillum.

Phlogosin was separated by Leber from cultures of staphylococcus aureus. It causes inflammation when injected.

Dimethylamin has been found in sausage and in fish.

Triethylamin, *prophylamin*, *tyrotoxicon*, *etc.*, also deserve mention here, though it may be hard to assign them their exact positions in such a classification.[1]

As a positive demonstration of the formation of ptomaines by bacterial action there are perhaps no experiments more illustrative and convincing than those of Poehl. It is known that most at least of these alkaloids give color reactions with various salts, especially with those of iron.

Poehl mixed very small proportions (0.05%) of perchloride of iron and ferro-cyanide of potassium with his nutrient media, and then cultivated various organisms thereon. In some cases slowly, in some rapidly, the color reaction appeared along the needle streak. Inasmuch as the resulting Berlin-blue, due to the reducing power possessed by the microbes, only forms in a slightly acid medium, the acid had sometimes to be added to previously alkaline or neutral gelatine jelly in which alone certain bacteria will grow. On the addition of nitric acid to cultures of cholera spirilla there developed beside the Berlin blue a reddish hue, which is also the case when these organisms grow on jelly free from either of these salts; this is probably identical with the skatol derivative found by Brieger in the urine of certain patients.

Poehl, by the way, observes that the Finkler-Prior bacillus needs a smaller proportion of acid to produce a similar reaction than Koch's spirillum, and recommends on these grounds the administration of oxidizing substances, like peroxide of hydrogen or permanganic acid, in order to check the formation of ptomaines and decompose those already formed —*Lancet*, October 30, 1886, p. 830.

But I must hasten along to consider the more exclusively surgical topics to which I desire to invite your attention throughout the remainder of this evening, and for the balance

[1]For further informaton the reader is advised to consult the excellent little monographs of Vaughan and A. M. Brown.

of this series of lectures. It is mainly to the matter of the surgical infectious diseases that this course is devoted, in other words to the mutual reactions of animal and vegetable cells.

Neelsen has divided the infectious diseases generally according to their bacteriological peculiarities, as follows:

1. General acute mycoses of the blood. (Anthrax, septicæmia of mice, etc.)

a. Toxic (Septicæmia.)

b. Intermittent. (Relapsing fever.)

2. Localized bacterial infections.

a. Local, with secondary general poisoning. (Putrid fever, cholera, tetanus.)

b. Local, with the general characteristics of inflammation, (Pneumonia, malignant œdema.)

c. Local with necrobiotic tendencies. (Hospital gangrene, progressive necrosis.)

d. Local, with pyogenic tendencies. (Suppuration.)

3. Mycoses of the blood with secondary local lesions. Measles, rötheln, scarlatina, variola, diphtheria, osteomyelitis, acute rheumatism, chicken-pox, cholera.

4. Mycoses with tissue proliferation; or the infectious granulomata.

This classification is logical providing it be quite correct, but it is questionable whether the diseases included in his third and fourth classes are in effect *mycoses*, and whether they are not due to some other parasitic form of life than the mycotic. Be this as it may those troubles which concern us at present are undoubtedly mycotic in origin, and we need only discuss some of their general phases before proceeding to special forms. And first of all and among the most important are:

Conditions Predisposing to Infection.—These conditions must be studied on the part of the body infected and on the part of the organism which produces the infection. First of these it must be laid down as a general rule that the normal healthy tissues of the human body neither harbor infectious organisms nor favor their development when introduced. In other words, the highest type of tissue vitality

presupposes a condition which is inimical to the action of any pathogenic bacterium. Furthermore, that such organisms, when introduced by accident into the circulating fluids of such a typically healthy body, are quickly destroyed in the circulation or in the tissues. Certain organisms disappear from the blood with remarkable rapidity, others are deposited in various tissues or organs where they are quickly disposed of, while yet others probably are excreted through some one of the various emunctories. When organisms disappear with such rapidity from the blood, it must be because they are quickly destroyed. Within the past year a number of papers have been published with reference to the antiseptic properties possessed by blood serum. It is well known that the blood serum of different animals varies very much in this capability as well as in its action with regard to different species. That the serum of rats' blood possesses a high degree of resistance in this direction has long been demonstrated by numerous laboratory experiments. Indeed so resistant is the common rat to most of the bacteria which are pathogenic for the human species, that extensive wounds can be inflicted upon them and not only no dressing be applied, but every opportunity for septic infection afforded, and still without the slightest apparent effect. Numerous experimenters have injected into the venous circulation various species of known organisms, and then have made or attempted to make cultivations from the blood at intervals varying from a few hours to a few days. It has been found that the rapidity with which they disappeared from the blood varied with the species employed, and according as it was or was not spore-bearing.

According to Wyssokowitsch, when small quantities of spirillum tyrogenum, a non-pathogenic and non-spore-bearing bacterium, were injected in the blood stream they were found in greatly diminished numbers after five minutes, and had completely disappeared in seven. In other cases spores were rapidly deposited from the blood but retained their vitality for several days. In the case of bacillus subtilis, a few were found alive even after seventy-eight hours. Apparently they were deposited in the endothelial cells of the smaller vessels and chiefly in the spleen. The streptococci pyogenes, which do

not exert a pathogenic action when introduced into the blood of rabbits in small numbers, were much reduced in number after seven hours, and disappeared after fifty.

From Wyssokowitsch's researches it would appear that organisms which do not rapidly die are deposited like particles of pigment; thus anthrax bacilli, introduced in moderately small quantities into rabbits, were found to have disappeared from the blood after twenty-four hours, though they were present in large numbers in the spleen and liver. That organisms may be excreted by the kidneys is shown by various observations, and, as Cheyne points out, it affords a very plausible explanation for certain cases of pyelitis and bacteruria occurring in patients who have never had any instrument passed, and whose ureters and bladders are perfectly normal. The explanation being that these organisms had entered the blood in a living state, had been excreted by the kidneys, and had afterwards found a suitable culture medium in the urine and grew in the pelvis of the kidney, or in the bladder. Thus Ogston states that he has found micrococci in the urine of patients suffering from septicæmia, though these patients apparently had no disease of the urinary organs. This statement seems quite positive, although some have denied the excretion of bacteria by the kidneys, and claim that they only appear in the urine after rupture of blood vessels. So, too, in pyæmia and some other diseases, for example in Ribbert's experiment with aspergillus. There is a marked tendency for the organisms to locate in the kidney, which would seem to indicate some functional or anatomical attraction by which they are drawn thither. Ribbert in his investigations concerning the cocci of osteomyelitis in the blood, found that after twenty-four hours they could be demonstrated in all the organs by Gram's method, but that later they disappeared from all except the kidney. Experiments elsewhere alluded to in these remarks demonstrate their excretion by the mammary glands, and are of interest in that they show that the organisms which cause abscesses of these glands may be deposited there from the blood, although undoubtedly the majority of abscesses of the breast are caused by the inward spread of bacteria from the surface. The frequent occurrence of abscesses, especially

metastatic, in the parotid gland, after suppuration in other parts of the body, finds here also, perhaps, its most easy explanation. Passet has even stated that cocci were excreted through the conjunctiva in the case of mice and his statement is confirmed by Longard.

Embolism, as a factor in provoking suppuration.—Attention has already been called to the large part played by emboli in surgical inflammations and affections, since there is no limit inside the living body to which infected emboli cannot be transported. Ribbert, while studying the death of fungi in the body, met some beautiful demonstrations in this direction. On comparing his experiments with aspergilli with those made with mucor, he found that in the former case deposits were formed in various organs and muscles, while the spores of the latter gave rise to deposits in organs only, the muscles being not affected. Referring this discrepancy to the relative size of the spores, the mucor spores being much smaller and passing more easily through the capillaries, he endeavored to increase their size before their introduction into the blood, and so kept them for a short time in a nutrient fluid. In consequence, they swelled up and commenced to sprout, and then he injected them into the circulation, when he found no difference between his results. The inference to be drawn from these experiments is very obvious, showing that organisms will or will not obstruct the capillaries in proportion to their size. Working in the same direction Ribbert found that the staphylococci would pass through the circulation, to be arrested in the kidneys, but that if pyogenic cocci were attached to larger particles which could not pass the capillaries, he could only produce myocarditis and endocarditis. For this purpose he cultivated the microbes on potatoes, and in removing them for experiments secured a mixture of potato granules and bacteria. If the particles of potato were very fine, only myocarditis resulted; if they were grosser, endocarditis appeared as well. Bonome studied nine cases of gangrene of the lung in man, and discovered staphylococci in all of them. Injecting cultures of these organisms into the blood of rabbits, he failed to cause any gangrene there, but by mixing them with very fine pieces of elder pith, and then injecting this mixture in the jugular vein,

he produced numerous embolic lesions in the lungs, which led to coagulation necrosis and extensive gangrene, while injections of fragments of pith alone produced no effect. So also, Pawlowsky found that simultaneous injection of sterilized cinnabar and of cultivations of staphylococcus aureus produced abscesses in various organs and in fact typical pyæmia.

General depression of vitality.—This has been recognized as a cause predisposing to suppuration for centuries, long before its active causes were thought of. Thus by administering large doses of phosphorus for some time to animals, such changes are produced.

Thus too such conditions as those brought about by starvation, by overwork, by vitiated food, by exposure, possibly even by mental worry, will so far reduce the vulnerability of previously healthy tissues that they succumb much more readily to bacterial infection. Such experiments as those made by Arloing, Cornevin and Thomas, are more than suggestive. They, inoculated some frogs with rauschbrand, and placed them with others not inoculated in vessels containing water at 22 C. After fifteen to thirty hours the inoculated frogs died, and in their lymph-sacs the rauschbrand bacilli were still active and virulent, while the uninoculated frogs remained well. In contrast with this, other frogs inoculated with the same germs, but kept in cold water, were unaffected.

The experiments of Charrin and Roger (*Arch. de Physiol.*) show that great fatigue favors infection. Animals that have been violently exercised died in shorter time, after inoculation with symptomatic anthrax, than those that had not been fatigued.

Local depression of vitality.—This is a cause more easily recognized, at least, if not more generally met with. When a given part has been deprived for a time of its natural blood supply, bacteria grow in that part much more readily than if such supply had not been interfered with. Thus, according to Cornil, a septic nephritis is readily obtained by ligating the renal arteries for some hours, then removing the ligature and injecting pyogenic organisms in the blood. The experiments made by Chauveau, termed the *bistournage*, point unmistakably in the same direction. Heubner's experiments in artifi-

cially producing diphtheria are most demonstrative. He ligated the vesical arteries for two hours, by which he produced intense congestion and submucous œdema of the fundus of the bladder, in consequence of which the epithelial cells died. After removing the ligature and thus restoring the circulation, there was copious exudate with coagulation necrosis. He found that if at the same time that he restored the circulation septic bacteria were injected into the blood, they accumulated in large number at the seat of these changes, it being only necessary that comparatively large numbers should be introduced. It is also stated by Cornil that if a slight nephritis is set up, either by cantharides or in some other way, and if then pyogenic organisms are injected into the blood, a septic peritonitis occurs.

Inflammation.—Obviously this is the most conspicuous illustration of local depression of vitality, and has long been recognized as preceding most every suppuration. Cheyne divides inflammation into three stages, the first including all the phenomena up to and including exudation; the second the substitution of granulation tissue for that originally attacked, and the third comprising the cessation of irritation and the changes which lead to the formation of a scar. During the first stage the natural vital activity of the part is suspended, and it is usually during this stage that organisms enter. It has been found that pyogenic cocci are not as likely to settle and infect a part which is acutely inflamed as in one where inflammation is less severe, where, apparently, they most usually pass out of the blood vessels. Thus Rinne, in experiments to be referred to later, found that a violent inflammatory action did not produce a point of least resistance, but that a slighter injury or disturbance, such as might be caused by the chemical products of bacteria, sufficiently weakened the part to enable the organisms to grow in it. Thus acute osteomyelitis and local tubercular disease much more often follow an injury of slighter severity, and very seldom occur after an extensive lesion. Fractures in consumptives are seldom if ever followed by local tuberculosis, while slight sprain is frequently assigned as the cause of such a process.

Cold.—A brief or long exposure to cold is so often men-

tioned as a cause for existing inflammations that it ceases to have much weight with the careful observer. It is only by careful experiment upon animals that its etiological importance can be determined. Lassar shaved a number of rabbits, and so long as he kept them at a suitable temperature they remained in good health. If plunged into ice cold water for from one to three minutes, and then carefully dried and warmed again, they almost always developed albuminuria with hyaline casts and with elevation of temperature. These animals often recovered to suffer in the same way again when similarly exposed. Microscopic examination showed that they had developed an interstitial nephritis. As more directly bearing upon our subject, the experiments of Grawitz on the relation of peritonitis to cold must here be mentioned. He shaved the abdomens of young animals, covered them for a short time with warm compresses, and then allowed a draught of ice cold air to play on the parts for twenty to forty minutes, and yet without noticeable effect.

Injury.—Injury acts in two ways. First by producing the first stage of inflammation, secondly by causing effusion of blood, and permitting an escape of any pyogenic cocci which may be there circulating, at a point where they may find a quiet medium suitable for their development. Prudden's studies of endocarditis have well shown the effect of injury, which is in large measure due to loss of resisting power of the endothelial and connective tissue cells. Since every wound must be followed at least by a conservative amount of inflammation it can be seen how operation wounds should be really included among injuries. Experimental work with symptomatic anthrax, which is only produced by bacilli acting in the tissues and not in the blood, affords ample illustration. If the bacilli of this disease are injected into the blood, the animals remain well and the bacilli soon disappear. But if immediately after their injection, a bruise be inflicted on some part of the body, by the aid of which the bacilli may escape from the vessels, soon the characteristic tumors form and the disease rapidly progresses to a fatal termination. Cheyne published the case of a drunkard in poor health suffering from albuminuria, who developed an abscess whenever and wherever he received a bruise. And every practitioner meets with analogous cases; in such instances the pyogenic cocci are alive in the blood, and the combination of lowered vitality, toxæmia and injury bring about the suppurative result.